Master of Medicine (MMed) in Anaesthesia

Clinical utility of B-type natriuretic peptide (NP) *in paediatric cardiac surgery – a* systematic review

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I, Dr Nura Afshani, hereby testify that the research reported in this study is a product of my own independent work and neither the whole work nor any part of it has been, is being, or is to be submitted for another degree to any other university. This work has not been reported or published prior to registration for the abovementioned degree.

Signature removed

Date: 02/02/2014

Part A: Study Protocol

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Title of project: **Clinical utility of B-type natriuretic peptide (NP) in paediatric cardiac surgery – a systematic review.**

Background

B-type natriuretic peptide (NP) is a biomarker that has gained widespread use in several patient populations and clinical situations. It is a hormone secreted primarily by ventricular myocytes in response to myocyte stretch or ischaemia. The physiological role played by this biomarker is to adapt to conditions of both pressure and volume overload of the heart. It reduces sympathetic activation resulting in vasodilatation, and it counter-regulates the renin-angiotension-aldosterone axis resulting in natriuresis and diuresis. Cleavage of the parent prohormone produces the active form of the hormone (BNP) and, in equimolar proportions, the biologically inactive form (NT-proBNP)

In clinical practice, NP has been shown to have diagnostic, prognostic and therapeutic value in adult patients with cardiac failure. In the surgical setting, NP is strongly predictive of adverse cardiac outcome in patients undergoing cardiac and non-cardiac, particularly vascular surgery.

Data on the use of NP in the paediatric population is growing. Studies have used NP as a diagnostic tool in a number of conditions including cardiac failure, cardiac transplantation rejection, cardiotoxicity of chemotherapeutic agents, vascular disorders such as Kawasaki disease and in pulmonary hypertension.

NP has also been used in the diagnosis, management and follow-up of paediatric patients with various types of congenital heart disease. The use of NP as a predictor of postoperative outcome following corrective or palliative cardiac surgery has also been investigated.

An important issue in the paediatric population has been the identification of reliable reference values for BNP and NT-proBNP in the various age categories, namely neonates, infants and older children. Recently, such reference values have been proposed.

Aim

The main objective of this study is to determine by way of a systematic review and meta-analysis, the utility of the novel biomarker B-type natriuretic peptide (NP) in predicting outcome in paediatric patients undergoing cardiac surgery for congenital heart diseases. Ultimately this study could pave the way for further well-conducted prospective trials to be carried out at Red Cross Children's Hospital.

The research questions that will be posed are:

1. Does preoperative natriuretic peptide (NP) level, either BNP or NT-proBNP, correlate with clinical and/or echocardiographic severity of congenital cardiac disease?
2. Do preoperative and postoperative NP levels predict early postoperative outcome (30-180 days)?
3. Do preoperative and postoperative NP levels predict longer term outcome (years)?

Subgroups that will be selected *a priori* for subgroup analysis are;

1. patients with and without pulmonary hypertension secondary to congenital heart disease,
2. patients with cyanotic versus acyanotic congenital heart disease,
3. age at the time of surgery.

Methods

Study design

This study is a systematic review and meta-analysis. The Cochrane Handbook for *Systematic reviews will be used as reference material to guide the conduct of this project.* The format of the dissertation will follow that of the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.

Study identification and selection

A literature search will be conducted using three electronic databases – Pubmed/MEDLINE, EMBASE and Cochrane. The search terms to be used will be "paediatric" or "pediatric" and "B-type natriuretic peptide". The date(s) on which the search was conducted will be specified to facilitate replicating the search. Any studies identified by hand-searching of journals and *consulting reference lists of papers will be indicated. The principal investigator and another* independent investigator will review the literature search abstracts and assess eligibility of the studies based on predefined inclusion and exclusion criteria (see below). This will be followed by full text review to confirm eligibility of the identified citations. To assess methodological quality of the included studies, a modified version of the Cochrane Collaboration endorsed checklist, the Recommended quality items derived from QUADAS tool[1], will be employed (see Appendix 1).

Data extraction

Data will be collected using Excel spreadsheet software. The following data will be extracted:

- Study reference: author, title, date.
- Study characteristics: study duration, type of study (retrospective or prospective observational, or randomised controlled trial), provider and outcome assessor blinding, other potential confounders and validity criteria.

- Participant characteristics: age, sex, type of congenital heart disease e.g. cyanotic, acyanotic, mixed, obstructive, complex and presence of secondary pulmonary hypertension.
- Outcome measures and results: type of NT assay used, reference values, outcome definitions e.g. mortality, heart failure, right ventricular function, exercise tolerance, etc. We will contact corresponding authors for any missing data. The data extracted independently by both investigators will be compared and any discrepancies resolved through independent adjudication by the supervisor and co-supervisor.

All studies reporting on BNP or NT-proBNP levels pre- and/ or postoperatively in paediatric patients who are to undergo, or have undergone, corrective or palliative surgery for structural congenital heart disease will be included. We will set a maximum age limit at time of surgery at 18 years of age. Studies to be excluded will be: non-human, non-English, reviews, comments and letters to the editor. We will also exclude data related to cardiac transplantation as the indication for cardiac transplantation includes not only structural congenital heart disease but many other causes of end-stage heart failure. RevMan 5.1 software will be employed for the statistical analysis.

Research expectations

This study will not require laboratory access or field work. I have access to UCT electronic databases, the Cochrane Handbook and to RevMan 5.1 software. The intention is to submit this paper for publication. The precise journal has not been decided upon although I will preliminarily adopt the referencing format stipulated by Pediatric Anesthesia. In terms of authorship, the first and corresponding author will be myself. The co-authors will be Dr Simone Schülein, Dr Bruce Biccard and Professor Jenny Thomas.

Acknowledgements

I have asked Dr Bruce Biccard to co-supervise this meta-analysis as his guidance throughout the process, and particularly with regard to the statistical analysis, will be most helpful.

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Appendix 1. Checklist for the assessment of study quality[1]

1. Was the spectrum of patients representative of the patients who will receive the test in practice? (i.e. the patients have structural congenital heart disease and are to have or have had surgical correction/palliation)
2. Is the reference standard likely to classify the target condition correctly? (i.e. clinical and echocardiography criteria used)
3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (i.e. *NP level taken at time of preoperative and postoperative clinical/echocardiographic* evaluation)
4. Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? (all patients were evaluated clinically/ using echocardiography)
5. Did patients receive the same reference standard irrespective of the index test result? (differential verification avoided i.e. the pathology was present regardless of the NP result)
6. Was the reference standard independent of the index test (i.e. NP levels were not used in preoperative diagnosis)
7. Were the reference standard results interpreted without knowledge of the results of the index test? (NP results blinded to preoperative severity and postoperative outcome)
8. Were the index test results interpreted without knowledge of the results of the reference standard? (NP results interpreted blind of preoperative and postoperative findings)
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (relevant clinical information including patient age)
10. Were uninterpretable/ intermediate test results reported? (not applicable to this review)
11. Were withdrawals from the study explained? (e.g. follow-up loss)
12. Were cut-off values established before the study was started?
13. Is the technology of the index test unchanged since the study was carried out?
14. Did the study provide a clear definition of what was considered to be a 'positive' result?

Publication-ready manuscript

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Article category: paediatric cardiac surgery

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Abstract

Background

NP is a biomarker that has been used in the diagnosis, management and prognostication of a number of cardiovascular disorders in the paediatric population. The physiological role of this hormone is to allow the myocardium to adapt to stress or strain imposed by a volume and/or pressure load.

Objective

The aim of this study was to determine the utility of preoperative and postoperative NP to predict outcome in paediatric patients undergoing cardiac surgery for structural congenital heart disease (CHD).

Method

We conducted a systematic review by searching three electronic databases using the search terms 'paediatric' or 'pediatric' and 'B-type natriuretic peptide'. Thirty-nine peer-reviewed papers were included in the study.

Results

Preoperative NP levels were associated with the severity of cardiac failure in several studies. Preoperative NPs also correlated with early postoperative outcome measures such as duration of cardiopulmonary bypass, duration of mechanical ventilation, presence of low cardiac output syndrome, length of stay in intensive care unit (ICU) and in one study, death. Postoperative NPs showed a stronger correlation than preoperative NPs to early postoperative adverse events. Postoperative NPs were also positively associated with long-term outcome. In patients with palliated univentricular hearts and repaired Tetralogy of Fallot, postoperative NPs were predictive of functional status and exercise capacity. In these patients postoperative NPs also correlated with echocardiographic and cardiac imaging changes, such as diastolic dysfunction, increased ventricular mass or volume and valvular regurgitation.

Conclusion

Postoperative NPs show a stronger correlation than preoperative NPs to postoperative outcome in patients with CHD. NPs are also associated with long-term postoperative

functional outcome and echocardiographic findings. NPs provide a simple, non-invasive complementary tool to assess paediatric patients with CHD in the perioperative period as well as to assist in their long-term management and prognosis. NPs may guide the timing of interventions to treat surgical sequelae such as pulmonary regurgitation.

Keywords: B-type natriuretic peptide, paediatric, pediatric, congenital heart disease, cardiac surgery

Introduction

NP is a biomarker that has gained widespread use in several patient populations and clinical situations. It is a hormone secreted primarily by ventricular myocytes in response to myocyte stretch or ischaemia. The physiological role played by this biomarker is to adapt to conditions of both pressure and volume overload of the heart. It reduces sympathetic activation resulting in vasodilatation, and it counter-regulates the renin-angiotension-aldosterone axis resulting in natriuresis and diuresis. Cleavage of the parent prohormone produces the active form of the hormone which is abbreviated to BNP in this paper and, in equimolar proportions, the biologically inactive form, N-terminal - pro B-type natriuretic peptide (NT-proBNP).(1)

In clinical practice, NP has been shown to have diagnostic, prognostic and therapeutic value in adult patients with cardiac failure.(2-5) In the surgical setting, NP is strongly predictive of adverse cardiac outcome in patients undergoing cardiac and non-cardiac, particularly vascular surgery.(6-8)

In the paediatric population, studies have used NP as a diagnostic tool in a number of conditions including cardiac failure, cardiac transplantation rejection, cardio-toxicity of chemotherapeutic agents, vascular disorders such as Kawasaki disease and in pulmonary hypertension.(9,10)

NP has also been used in the diagnosis, management and follow-up of paediatric patients with various types of congenital heart disease (CHD).(11-13) The use of NP as a predictor of postoperative outcome following cardiac surgery has also been investigated.(14-17)

Objectives

The main objective of this systematic review was to determine the utility of NP to predict outcome in paediatric patients undergoing cardiac surgery for CHD.

We addressed the following research questions:

1. Does preoperative NP level correlate with clinical and/or echocardiographic severity of CHD?
2. Do preoperative and postoperative NP levels predict early postoperative outcome (30-180 days)?
3. Do preoperative and postoperative NP levels predict long-term outcome (years)?

Subgroups that we selected *a priori* for subgroup analysis were:

1. patients with and without pulmonary hypertension secondary to CHD,
2. patients with cyanotic versus acyanotic CHD,
3. age at the time of surgery.

Methods

Study design and protocol registration

We undertook a systematic review and meta-analysis. The conduct of the study was guided by the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy.(18) The format follows the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) guidelines.(19) The study protocol has been registered with PROSPERO and can be viewed using the following web link: http://www.crd.york.ac.uk/PROSPERO. The reference number is CRD42012003513.

Eligibility criteria

We included all studies reporting on BNP or NT-proBNP levels pre- and/ or postoperatively in paediatric patients who had undergone, or were due to undergo, corrective or palliative surgery for structural CHD. We excluded papers that were non-human studies, non-English, reviews, comments and letters to the editor. We also excluded data related to cardiac transplantation as the indication for cardiac transplantation includes many causes of end-stage heart failure.

Information sources and search strategy

We conducted a literature search using three electronic databases- Pubmed/MEDLINE, EMBASE and Cochrane. The search was performed initially on the 4th of May 2012 using only Pubmed/MEDLINE and then repeated on the 31st of July 2012 to include EMBASE and Cochrane. No additional citations were retrieved on Pubmed/MEDLINE. The search terms used were "paediatric" or "pediatric" and "B-type natriuretic peptide". We also consulted reference lists of identified papers and hand-searched journals of interest.

Study selection

Two independent investigators (NA and SS) reviewed the abstracts of the literature search and assessed eligibility of the studies. This was followed by full-text review by NA and SS to confirm eligibility of the identified citations.

Data extraction

Data was extracted using Mac Microsoft Office 2008 Excel spreadsheet software. The following data were extracted:

- Study reference: author, title, date.
- Study characteristics: study duration, type of study, provider and outcome assessor blinding and validity criteria.
- Participant characteristics: age, sex, type of congenital heart disease and presence of secondary pulmonary hypertension.
- Outcome measures and results: type of NP assay used, reference values, outcome definitions.

We contacted corresponding authors via email for any missing data. The data extracted independently by both investigators was compared and any discrepancies resolved through independent adjudication by BB and JT.

Study quality assessment

To assess methodological quality of the included studies, a modified version of the Cochrane Collaboration endorsed QUADAS checklist (20) was used.

Data analysis

Statistical analyses of individual patient data obtained from authors were performed using the Statistical Package for the Social Sciences (SPSS) version 19 (SPSS Inc., Chicago, IL, USA). All categorical data were analysed using descriptive statistics and either the Fisher's Exact Test or Pearson's Chi-square test where appropriate. All continuous data were analysed using descriptive statistics and compared using independent samples t-test, ANOVA test, Mann-Whitney U-test or Kruskal-Wallis test where appropriate. Receiver operating characteristic (ROC) curve analysis was performed where possible.(21) The optimal test cut-point value is the point which maximises the rate of true positives while minimising the rate of false positives. This was defined by ROC statistics using a 1:1 weighting of sensitivity and specificity and the point determined by the value with the minimum distance when using the formula: Distance = $(1- \text{Sensitivity})^2 + (1- \text{Specificity})^2$. We chose this method over the Youden index as minimizing misclassification was given a higher priority than appropriate classification.(22) The screening cut-point was determined at a sensitivity closest to 95% while optimising specificity, and conversely the diagnostic cut-off point was determined at a specificity closest to 95% while optimising sensitivity.(23) We set the significance level at $p=0.05$. The kappa statistic was used to assess inter-rater agreement.

Results

The electronic search identified 429 papers. Of these, 44 papers fulfilled our inclusion criteria. We were unable to retrieve the full-text paper of six of the citations (of which five were conference abstracts), even after contacting corresponding authors as well as co-authors. We excluded one case report. One author(24) referred us to an additional paper, which we were able to include in our study.(25) Another paper published after our original search, fulfilled our inclusion criteria.(26) This systematic review therefore includes 39 peer-reviewed papers(13-17,21,24-56) (Figure 1). We contacted corresponding authors in order to obtain individual patient data for our analysis. Where no response was received from corresponding authors, attempts were made to contact co-authors. We obtained additional patient data for nine studies.(15,21,29,30,32,38,46,48,49) Two of these datasets did not included corresponding outcomes and it was therefore not possible to include these two studies in our statistical analyses.(30,48) Figure 1 demonstrates the study selection process. The kappa coefficient for abstract review was 0.43 while that of the full-text selection was 0.97.

Insert Figure 1 here

The patient characteristics and study quality scores are shown in Table 1. Studies looked at patients with various forms of univentricular heart(21,24,25,28,35-38,42,44,45,48,52,56), Tetralogy of Fallot (27,30,31,39-41,43,47,51,54,55), left-to-right shunt (17,46), transposition of the great arteries (33,34,53), aortic coarctation(50) or mixed cardiac lesions. (13-16,26,29,32,49) We used a modified QUADAS study quality checklist (see Appendix 1). (20) In twelve of the studies NP assessment and outcome assessment were blinded.(14,16,17,27,32,36-40,49,53). The breakdown of the individual study scores is provided (see Appendix 2).

Insert Table 1 here

The details of the NP assays used are shown in Table 2.

Insert Table 2 here

Natriuretic peptide levels and clinical and/or echocardiographic severity of CHD

Five studies reported the association between NPs and clinical or echocardiographic severity of cardiac failure.(15,17,46,49,56) Three papers showed a positive association.(15,17,49) Preoperative BNP levels were higher in patients who were treated for heart failure compared with patients who were not in heart failure prior to cardiac surgery (median 82.6pg/ml versus 14.7pg/ml; p<0.006)(49) Patients in cardiac failure preoperatively had significantly higher preoperative logNT-proBNP levels than those who were not in heart failure (3.42+/- 0.84log vs 2.53+/-0.77log respectively; p<0.001).(15) In patients with left ventricular volume overload due to ventricular septal defect or complete common atrioventricular canal, preoperative NT-proBNP levels were significantly higher than controls (mean 3085 +/- 4046pg/ml versus 105+/- 78 pg/mL; p=0.01).(17)

In patients with left-to-right shunt preoperative BNP levels could not discriminate between patients with or without clinical heart failure assessed using a modified Ross score (p=0.287).(46) In univentricular heart patients scheduled for a Stage I (Norwood) operation there was no correlation between NT-proBNP levels and systemic ventricular function or degree of atrioventricular valve regurgitation.(56)

Natriuretic peptides and prediction of early (30-180 days) postoperative outcome.

Preoperative NPs and early postoperative outcome. Nine studies reported the association between preoperative NPs and early adverse postoperative outcome.(15-17,26,28,29,38,49,53) Five studies including a total of 306 patients showed a positive association(15-17,29,49) and four studies including a total of 201 patients showed no association(26,28,38,53).

Preoperative NPs predicted higher mortality in one study(29) as well as the presence of low cardiac output syndrome(29,49), longer cardiopulmonary bypass time(17), longer duration of mechanical ventilation (17,49) and longer length of stay in ICU (15,17) and in hospital(17). The study findings are summarised in Table 3.

Insert Table 3 here

There was no significant correlation between preoperative BNP levels and adverse outcome in patients with univentricular heart undergoing palliation(28,38), transposition of the great arteries undergoing arterial switch(53) as well as in a mixed cohort of patients with various cardiac lesions(26).

Postoperative NPs and early postoperative outcome. Twelve studies reported on the predictive value of postoperative NPs and early postoperative outcome.(14-17,26,28,29,32,38,46,49,53) Peak postoperative NP levels were predictive of duration of cardiopulmonary bypass, duration of mechanical ventilation, length of stay in ICU, serum lactate, inotropic use and presence of low cardiac output syndrome as well as death and unplanned surgical intervention. In a study of patients with left-to-right shunt, the change in pre- to postoperative BNP showed a significant correlation with the reduction in left ventricular end-diastolic dimension. Table 4 summarises the individual study findings.

Insert Table 4 here

Natriuretic peptides and prediction of late (years) postoperative outcome.

A total of twenty one papers reported the association between NPs and long-term postoperative functional status as well as echocardiographic or cardiac magnetic resonance imaging indices of cardiac structure and function.(21,25,27,30,31,33-36,39,40,42-45,47,48,50,51,54,55)

Two studies reported the association between NPs and patients with transposition of the great arteries.(33,34) One study showed that BNP levels correlated significantly with right ventricular function following atrial switch(33) while another did not demonstrate any relationship between BNP levels and right ventricular function and exercise capacity.(34)

One small study demonstrated a correlation between BNP and left ventricular mass and diastolic dysfunction in patients following repair of aortic coarctation.(50)

NP levels and subgroup analysis

Only three studies specified whether patients were cyanotic.(15,29,35) Carmona et al. showed that postoperative NT-proBNP was an independent predictor of low cardiac output syndrome in their mixed cohort of patients. Low cardiac output syndrome occurred more commonly in the cyanotic versus the acyanotic group (19 patients versus 3 patients, $p<0.007$). However, from this study, it was not possible to comment on the association of low cardiac output syndrome with NT-proBNP in the cyanotic versus the acyanotic subgroups. In the study by Hager et al. cyanotic patients had significantly higher NT-proBNP levels than those without cyanosis but no difference in outcome compared with acyanotic patients was reported. We found no data on secondary pulmonary hypertension.

Nine studies reported the association between NPs and age at time of surgery.(14-17,25,26,49,51,54) Overall, these studies reported an inverse relationship between NPs and age, in keeping with age-related NP levels in the normal paediatric population. These studies varied in the form of the biomarker (BNP versus NT-proBNP) and assay used as well as in the type of CHD evaluated. It was therefore not possible to combine datasets.

Discussion

The main findings of this systematic review are that in patients with CHD, NP levels are associated with preoperative clinical status as well as with adverse events in the perioperative period. NP levels also correlate with long-term functional status and outcome.

In patients with structural CHD the range of NP levels varies widely depending on a number of factors including age at time of surgery, type of lesion, stage and type of palliation and duration of CPB.(11-13,26).

Normal reference levels and cut-points in the paediatric population

In the paediatric population, age-specific normal NP levels have recently been established.(57-59) In healthy subjects levels are highest in the first four days of life followed by a sharp decline in the first week and a more gradual decline throughout the first month. Thereafter levels remain steady, without gender differences, until after the first decade.(58,59) To retain diagnostic accuracy, NP assays require age-specific cut-points.(57) Albers et al. showed that for NT-proBNP the 97.5th centile ranged from 320pg/ml (1-3years) to 115pg/ml (18years).(57) For BNP, Law et al. have proposed a BNP cut-point for neonates of 170pg/ml (sensitivity 94%, specificity 73%) and 41pg/ml for infants and older children (sensitivity 87%, specificity 70%) to diagnose patients with cardiovascular diseases including anatomic defects.(60) Cantinotti et al. proposed the concept of using two cut-points in the neonatal period based on centiles, although they were not prescriptive as to what the actual values should be.(11,59) Because there are a number of NP immunoassays available, it is important that well-validated assays with low inter-laboratory variability are used.(57)

Pattern of NP change following cardiac surgery involving cardiopulmonary bypass (CPB)

NP levels follow a characteristic pattern demonstrated in several studies. Peak postoperative levels occur most commonly between 6 to 24 hours postoperatively.(14-17,49) However, in the first few hours following cardiac surgery, NPs are at their lowest level, sometimes lower than baseline levels. This is due to a number of factors – during cardiopulmonary bypass,

NPs are broken down by C-receptors located on endothelial cells(15) and not resynthesized, NPs are removed from the circulation during ultrafiltration and following separation from cardiopulmonary bypass, it takes time for the heart to fill completely. Koch et al. demonstrated a second peak occurring around postoperative day 5.(14) It is important, therefore, to appropriately time postoperative NP sampling.

NP levels in different types of CHD lesions

A number of studies showed that prior to correction or palliation, lesions producing left-sided volume and/or pressure load such as ventricular septal defect are associated with higher NPs than lesions causing right-sided volume and/or pressure load such as Tetralogy of Fallot. Complex lesions including various types of unpalliated univentricular heart and transposition of the great arteries tend to have the highest NPs. This may be explained by varying degrees of haemodynamic stress or strain imposed on the myocardium.

In patients with univentricular heart, levels are significantly higher after Norwood Stage I palliation compared with controls. However, unloading of the systemic ventricle with Stage II (bidirectional cavopulmonary anastamosis/ Glenn shunt) and Stage III (total cavopulmonary anastamosis or atriopulmonary connection) palliation results in patients at these stages having levels similar to controls.(35,37). While non-neonates with left-to-right shunt and Tetralogy of Fallot had higher NPs postoperatively than preoperatively, in neonates with complex lesions such as univentricular heart and transposition of the great arteries preoperative NPs were actually higher than postoperative levels.(26) These findings again highlight the importance of taking into account patient age, type of cardiac lesion and stage of palliation or repair when evaluating the utility of NPs.

Utility of preoperative and postoperative NP levels in CHD.

Preoperative NPs reflect clinical status, specifically the presence and severity of cardiac failure. Although preoperative levels are associated with adverse postoperative outcomes such as death, duration of mechanical ventilation, length of stay in hospital and low cardiac

output syndrome, postoperative levels are more predictive of poor outcome in the early postoperative period. We presume that postoperative levels also take into account intraoperative factors such as surgical complexity or difficulty, bloodloss and duration of cardiopulmonary bypass as well as the degree of physiological reserve of the patient.

Postoperative NP levels also correlate with long-term outcome measures including exercise capacity, indices of subclinical ventricular systolic and diastolic dysfunction as well as valvular dysfunction particularly in patients with palliated univentricular heart and repaired Tetralogy of Fallot.

In both patients with repaired Tetralogy of Fallot and palliated univentricular heart, maximal exercise capacity is predictably reduced. However, the two groups show a distinct difference. The rise in NPs was significantly higher in patients with Tetralogy of Fallot than in controls indicating increased load or strain on the right ventricle.(31,39,47) In patients with univentricular hearts, post-exercise NPs did not rise as much as in healthy controls.(35,36,54) The authors concluded that the reduced exercise capacity in patients with univentricular hearts was not due to myocardial dysfunction but rather impaired pulmonary dilatation and blood flow with resultant restricted diastolic filling of the systemic ventricle.(35,36,54) In both patients with Tetralogy of Fallot and univentricular hearts, higher NPs predict poorer outcome or more complications. However, while measuring NPs after exercise in patients with repaired Tetralogy of Fallot is useful, resting NPs in patients with univentricular hearts appear to be sufficient in providing a measure of functional status.

NPs may be a helpful screening tool to detect pulmonary regurgitation, right atrial enlargement, right ventricular dilatation and/ or right ventricular dysfunction in asymptomatic patients post Tetralogy of Fallot repair and may help to determine the optimal time for pulmonary valve replacement.(30,31,39,43,54,55)

Limitations

The studies included in this review are of moderate to high quality. However, many were of small sample size. We obtained adequate individual patient data for seven studies. Some studies used outdated assay kits. Where different assays were used we were unable to compare results from different studies. Due to small sample size and heterogeneous outcome measures, there was insufficient data to conduct a meta-analysis of any of the outcomes of interest. We were unable to obtain the full-text of six papers. This leads to concerns regarding dissemination and other biases. However, these studies, comprising a total of 182 patients, were also of relatively small sample size and included a number of different types of CHD. It is unlikely that this would have enabled us to perform a meta-analysis or led us to significantly different overall results.

Conclusion

This systematic review demonstrates several correlations between NP levels and outcome in patients with CHD both before and after curative or palliative surgery. Postoperative NP levels show a stronger association to, and may be more predictive of, postoperative patient outcome than preoperative levels. However due to the wide range of cardiac lesions and other variables mentioned, this systematic review does not aim to provide convenient cut-points with which to accurately classify paediatric patients into different diagnostic or prognostic categories. NP levels correlate with long-term postoperative functional status and echocardiographic findings including markers of ventricular dysfunction and valvular dysfunction. Echocardiography remains a first-line investigation in patients with structural CHD. The measurement of NP levels may serve as a complementary simple, low-cost, non-invasive and, in many institutions, a more readily available tool to assist in the perioperative management of patients with CHD.

Acknowledgements

We thank Dr Reitze Rodseth for retrieving the full-text of several of the papers used in our review.

We thank Professor Jeffrey R. Fineman for providing us with additional study data for several papers.

We also thank Professors Fabio Carmona, Harold Bernstein and Alfred Hager as well as Drs Maria-Rosa Pérez-Piaya, Michael Paul and Iker Çetin for the additional study data, which they provided. We thank Dr Lynn Sleeper for referring us to an additional paper that fit our inclusion criteria.

Disclosure of interests

We do not have any competing interests.

Contribution to Authorship

Conception (NA, JT), planning (NA, BB), data extraction (SS, NA), analysis (BB, NA) and write up (NA, BB, JT).

Ethics approval

Ethics approval was not required for this systematic review.

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Tables/ Figure Legends

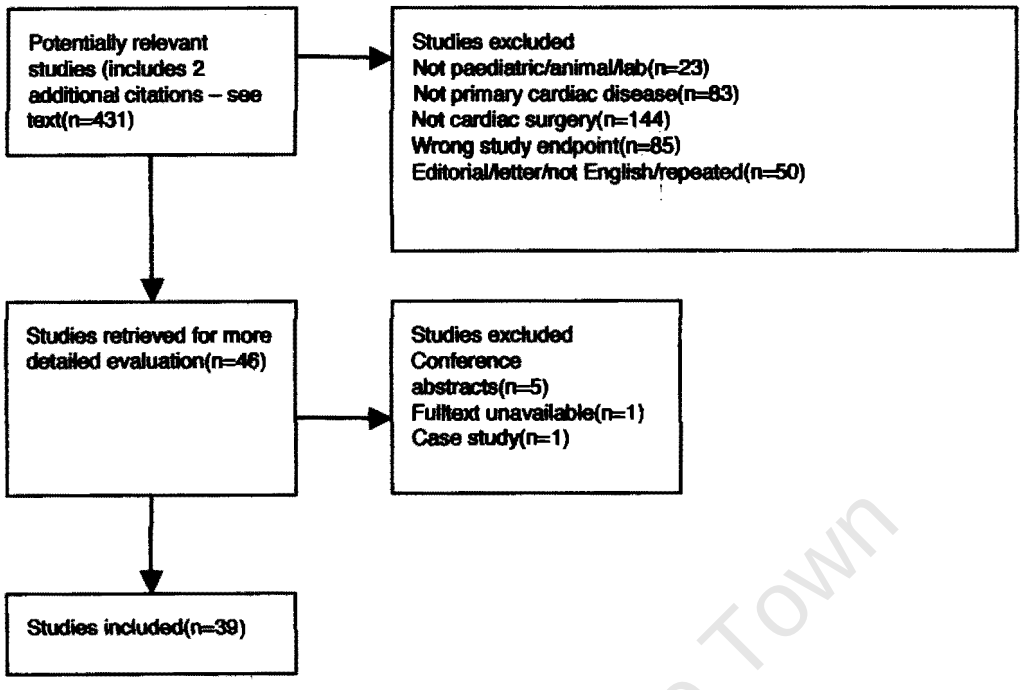

Figure 1. PRISMA flow diagram showing the study identification process

Author	Type of Study	Type of CHD	Age Median(iQR or range) or Mean(+/-SD)	Number of patients	Outcome assessed	Study quality score (out of 13)(20)
Tavli(2010)(50)	Cross-sectional observational	Coarctation	8.5+/-4yrs	14	LV performance; LV mass	10
Paul(2009) (46)	Prospective observational	LRS	6.0(1.3-13.6)mths	21 preop; 14 postop	Post-operative CF: Ross score, LVEDDz	9
Walsh(2008)(17)	Prospective observational	LRS	4.0(1–36)mths	VSD: 30; CCAVC: 8	CPB time; MV; LOS ICU; TISS	12
Amirnovin(2012) (26)	Prospective observational	Mixed	UH:9+/-8d;TGA:10+/-9d; LRS:10+/-2mths; ToF: 4+/-3mths	115 total;UH:24;TGA:11; LRS:55;ToF:25	Death/ surgical intervention; MV;LCOS;LOS in ICU	11
Carmona(2008)(29)	Prospective observational	Mixed	3.7 mths(5days -18mths)	46	Death; LCOS	10
Chikovani(2007)(32)	Prospective observational	Mixed	164+/-322days	10	Need for ECLS; death/unplanned operation	12
Koch(2006)(13)	Cross-sectional observational	Mixed	6.0+/-6.4yrs	288	Not defined	9
Niedner(2010)(16)	Prospective observational	Mixed	1(range 0-17)yrs	105	Death;cardiac arrest;ICU LOS;MV;LCOS;open chest	12
Pérez-Piaya(2011)(15)	Prospective observational	Mixed	Volume overload: 29(0.7-182)days; pressure overload: 0.6(0,2-180)days; cyanotic: 3.5(0.2-78)days	68	Death;prolonged PICU stay;MV; inotropic dose	11
Shih(2006)(49)	Prospective cohort	Mixed	331(1-5655)days	49	Preoperative CF; MV; LCOS	12
Koch(2007)(14)	Prospective observational	Mixed-	3.6+/-4.7yrs	65	Not defined	12
Cannesson(2007)(53)	Prospective observational	TGA	Complicated postop:9(6-12)days; simple postop:8(6-8)days	30	MV, LCOS	12
Chow(2008)(33)	Cross-sectional observational	TGA	19.7±4.0yrs	44	Systemic ventricular function	10
Garg(2008)(34)	Cross-sectional observational	TGA	Surgically corrected TGA: 25.5(15.2–36.5)yrs; Congenitally corrected TGA (ccTGA): 22.6(11.4–30.9)yrs	TGA: 17; ccTGA: 7	Exercise capacity; RV function (CMR&ERNA)	8
Apitz(2009)(27)	Cross-sectional observational	ToF	15.9yrs(mean)	16	RV contractile reserve	10
Cetin (2008)(31)	Cross-sectional observational	ToF	14.1 ± 4.4 yrs	25	Exercise capacity	10

Cetin (2009) (30)	Cross-sectional observational	ToF	14.1 ± 4.4 yrs	25	RV function; presence of PR	10
Ishii(2005)(39)	Prospective cohort	ToF	9.6+/- 3.3yrs	26	RV contractile reserve during exercise	11
Khositseth(2007)(40)	Cross-sectional observational	ToF	12.06 ± 2.54yrs	21	RV dilatation and function	12
Knirsch(2008)(41)	Prospective observational	ToF	11.7+/-3.5yrs	16	RV size; CF	11
Koch(2010)(54)	Retrospective cross-sectional & longitudinal	ToF	16.1+/-7.1yrs	130	CF;RV size; exercise performance	11
Luijnenburg(2012)(43)	Cross-sectional observational	ToF	21(+/-8)yrs	51	Exercise capacity;RA emptying;EDFF	11
Pietrzak(2009)(47)	Cross-sectional observational	ToF	13.5+/-2.7yrs	20	RV function during exercise	9
van den Berg(2009)(51)	Cross-sectional observational	ToF	15 (7–26) yrs	51	Ventricular functional reserve	11
Wand(2007)(55)	Cross-sectional observational	ToF	group A(<10yrs):mean7yrs; group B (>10 yrs): mean 16yrs	21	RV function;RV size	10
Atz(2011)(25)	Multicenter cross-sectional observational	UH	11.4 (9.0–14.6)yrs	546 (510 had BNP levels)	Exercise capacity; functional status; diastolic dysfunction; ventricular mass	8
Berry(2008)(28)	Prospective observational	UH	Norwood:4.4+/-1.5days; BCPA:5.2+/-0.7months; Fontan:2.7+/-0.6yrs	20	MV;inotropic support;hospital LOS	13
Eerola(2010) (56)	Prospective observational AND cross-sectional observational	UH	4 study points 1: 5(1-27)days; 2: 3.4(1.7-5.3)mths; 3: 1.02(0.7-1.1)yrs; 4: 2.05(1.74-3.5)yrs	Study point 1:19; 2:19; 3:12; 4:11. Cross-sectional arm: 11+21(32) preTCPC and 12 post TCPC.	Systemic ventricular function;AV valve regurgitation;death	10
Hager(2012)(35)	Prospective cohort	UH	16.3± 6.9yrs	66	Exercise capacity	11
Holmgren(2007)(36)	Prospective observational	UH	TCPC:14.6(12.5 to 17.9)yrs; Fontan: 32.1(15.6 to 54.2)yrs	TCPC: 6; Fontan: 9	Ventricular function after maximal exercise	12
Holmgren(2008)(37)	Cross-sectional observational	UH	Stage I: 0.5(0.5–0.9)yrs; Stage II: 3.0(1.6–3.7)yrs; Stage III:12.1(5.2–17.9)yrs	Stage I :10; Stage II:13; Stage III:15.	NP at various stages of palliation	12
Hsu(2007)(38)	Prospective observational	UH	BCPA: 7.6+/-9.3mths; TCPC: 76.9+/- 43.2mths	BCPA: 25; TCPC: 11	Death/ surgical intervention; LCOS;MV	13
Koch(2008)(42)	Retrospective	UH	13.8+/-5.8yrs	67	Death;ventricular function;AV valve function;arrhythmias	10

Man(2007)(44)	Cross-sectional observational	UH	13.7 ± 5.3yrs	35	Ventricular function	10
Ohuchi(2004)(45)	Prospective cohort	UH	low-age group: 11+/-3yrs; high-age group:19+-/5 yrs	97(TCPC 75, APC 22)	Cardiopulmonary capacity	8
Robbers-Visser(2009)(48)	Cross-sectional observational	UH	10.4(6.8–22.2)yrs	34	CF;arrhythmias;exercise capacity;ventricular mass	11
Sleeper(2006)(24)	Multicenter cross-sectional observational	UH	11.9+/-3.4yrs	546	Functional health status; ventricular function	7
Wåhlander(2012)(52)	Cross-sectional observational	UH	Stage I: 0.6(0.5–0.9)yrs; Stage II: 3.0(1.6–3.7)yrs	Stage I:7; Stage II: 10	Comparison of NP levels	12
Lowenthal(2012)(21)	Cross-sectional observational	UH(Rvs L)	R:16(2-80) mths; L:44(3-78) mths; indeterminate 60(56-66) mths	R: 51; L: 18; indeterminate: 2	Post-operative CF	12

APC: atriopulmonary connection; AV: atrioventricular; BCPA: bidirectional cavopulmonary anastamosis; BNP: B-type natriuretic peptide; CCAVC: complete common atrioventricular canal; CF: cardiac failure; CHD: congenital heart disease; CMR: cardiac magnetic resonance imaging; CPB: cardiopulmonary bypass; ECLS: extracorporeal life support; EDFF: end-diastolic forward flow; ERNA: equilibrium radionuclide angiography; ICU: intensive care unit; IQR: interquartile range; L: left; LCOS: low cardiac output syndrome; LOS: length of stay; LRS: left-to-right shunt; LV: left ventricle; LVEDD*z*: left ventricular end-diastolic dimension *z*-score; MV: mechanical ventilation; NP: natriuretic peptide including both BNP and NT-proBNP; NT-proBNP: N-terminal pro B-type natriuretic peptide; PICU: paediatric intensive care unit; PR: pulmonary regurgitation; R: right; RA: right atrial; RV: right ventricle; SD: standard deviation; TCPC: total cavopulmonary connection; TGA: transposition of the great arteries; TISS: therapeutic intervention score; ToF: Tetralogy of Fallot; UH: univentricular heart.;

Table 1. Characteristics of eligible studies and study quality assessment

Author	Biomarker	Diagnostic assay	Reference limit used & units
Amirnovin(2012) (26)	BNP	Biosite(Triage)	5-5000pg/ml
Apitz(2009)(27)	BNP	ADVIA Centaur BNP (Siemens)	pg/ml
Atz(2011)(25)	BNP	Shinogi (Rochester)	pg/ml
Berry(2008)(28)	BNP	Biosite(Triage)	pg/ml
Cannesson(2007)(53)	BNP	Biosite(Triage)	1-5000ng/L
Cetin (2009) (30)	BNP	Biosite(Triage)	pg/ml
Cetin (2008) (31)I	BNP	Biosite(Triage)	pg/ml
Chikovani(2007)(32)	BNP	Biosite(Triage)	pg/ml
Chow(2008)(33)	BNP	Biosite(Triage)	pg/ml
Garg(2008)(34)	BNP	Quest Diagnostics (California)	pg/ml
Holmgren(2007)(36)	BNP	Shionoria(Japan)	0-18.4ng/L
Holmgren(2008)(37)	BNP	NR I	0-18.4ng/L
Hsu(2007)(38)	BNP	Biosite(Triage)	pg/ml
Ishii(2005)(39)	BNP	NS	pg/ml
Koch(2006)(13)	BNP	Biosite(Triage)	pg/ml
Koch(2007)(14)	BNP	Biosite(Triage)	5-1300pg/ml
Koch(2008)(42)	BNP	Biosite(Triage)	5-5000pg/ml
Koch(2010)(54)	BNP	Biosite(Triage)	pg/ml
Man(2007)(44)	BNP	Biosite(Triage)	pg/ml
Niedner(2010)(16)	BNP	Biosite(Triage)	pg/ml
Ohuchi(2004)(45)	BNP	NR	pg/ml
Paul(2009) (46)	BNP	Biosite(Triage)	pg/ml
Shih(2006)(49)	BNP	Biosite(Triage)	5-5000pg/ml
Sleeper(2006)(24)	BNP	NS	NS
Wåhlander(2012)(52)	BNP	Shionoria(Japan);	0-18.4ng/L
Knirsch(2008)(41)	BNP and NT-proBNP	Biosite(Triage) and Roche(Elecsys)	ng/ml
Lowenthal(2012)(21)	BNP and NT-proBNP	Biosite(Triage) and Roche(Elecsys)	pg/ml
Wand(2007)(55)	BNP and NT-proBNP	ADVIA Centaur(USA) and Roche(Elecsys)	pg/ml
Carmona(2008)(29)	NT-proBNP	Biomedica(Vienna, Austria)	fmol/ml
Eerola(2010) (56)	NT-proBNP	Roche(Elecsys)	ng/ml

Hager(2012)(35)	NT-proBNP	Roche(Elecsys)	ng/L
Khositseth(2007)(40)	*NT-proBNP*	*Roche(Elecsys)*	*pg/ml*
Luijnenburg(2012)(43)	NT-proBNP	Roche(Elecsys)	pmol/L
Pérez-Piaya(2011)(15)	NT-proBNP	Roche(Modular AnalyticsE170)	pg/ml
Pietrzak(2009)(47)	NT-proBNP	NS	fmol/L
Robbers-Visser(2009)(48)	NT-proBNP	Roche(Elecsys)	pmol/L
Tavil(2010)(50)	NT-proBNP	Roche(Elecsys)	NS
van den Berg(2009)(51)	NT-proBNP	Roche(Elecsys)	pmol/L
Walsh(2008)(17)	NT-proBNP	Roche(Elecsys)	pg/ml

BNP: B-type natriuretic peptide (active form); NT-proBNP: N-terminal-pro BNP (inactive form);

NR:not reported; NS:not specified

Table 2. Characteristics of B-type natriuretic peptide assays

Author	Outcome measure	Findings
Shih et al.(49)	MV>48hrs, LCOS	BNP higher in patients with MV >48hrs (p=0.007) and LCOS (p<0.001)
Pérez-Piaya et al.(15)	PICU LOS>7days	NT-proBNP higher in patients with PICU LOS >7days (p=0.005) logNT-proBNP >3.4 predicted PICU LOS >7days (OR 8.25, 95% CI 2.45-27.73)
Carmona et al.(29)	In-hospital death, LCOS	NT-proBNP cut-point 4060pg/ml predicted in-hospital death (p=0.021, OR 6.4, 95%CI 1.1-35.7) and a cut-point of 3975pg/ml predicted LCOS (p=0.013, OR 5.7, 95%CI 1.5-21.3)
Walsh et al.(17)	CPB time, MV, hospital LOS and PICU LOS	NT-proBNP correlated with CPB time (*r=0.529, p=0.0006*), MV (r=0.445, p=0.005), hospital LOS (r=0.487, p=0.002) and PICU LOS (r=0.435, p=0.006)
Niedner et al.(16)	Death, cardiac arrest, ICU LOS > 28 days	BNP weak predictor of outcome measure. Five non-neonatal patients were identified that demonstrated a pre-operative BNP AUC of 0.83 (BNP of > 64 pg/mL yielded a sensitivity of 80% and a specificity of 85% specificity).

Table 3. Summary of studies showing positive association between preoperative NP levels and early postoperative outcome

AUC: area under the curve; CPB: cardiopulmonary bypass; LCOS: low cardiac output syndrome; LOS: length of stay; MV: mechanical ventilation; PICU: paediatric ICU; OR: odds ratio.

Author	Outcome measure	Timing of postoperative NP	Findings
Niedner et al.(16)	MV, inotropic requirement, duration of open chest, ICU LOS, hospital LOS	Peak (6- to 12-hr postoperative) and 24-hr average BNP	Levels correlated with all outcomes (r=0.51-0.65, all p<0.001).
Paul et al.(46)	Postoperative cardiac failure: modified Ross score, LVEDD*z* score	Months postoperatively	Reduction in BNP from pre- to postoperative levels correlated with reduction in LVEDD*z* score (p=0.049); no correlation between change in BNP levels and change in modified Ross score.
Koch et al.(14)	CPB duration, postoperative serum lactate	BNP measured daily postoperatively.	All levels correlated with CPB duration (r-0.58, p<0.001) and postoperative serum lactate (r=0.52, p<0.001).
Pérez-Playa et al.(15)	PICU LOS >7 days	Peak NT-proBNP	logNT-proBNP > 4.22 predicted PICU LOS >7 days (OR 12.29, 95% CI 3.47-43.5)
Carmona et al.(29)	LCOS	4-hr postoperative NT-proBNP.	NT-proBNP cut-point 3974pg/ml predicted LCOS (p=0.012, OR 5.7, 95%CI 1.5-21.3)
Chikovani et al.(32)	Poor outcome defined as death or unplanned surgical intervention.	BNP measured before and after trial of ECLS.	BNP trial/pre-trial ratio of >1 had a sensitivity of 80% and specificity of 100% for predicting poor outcome (p<0.05).
Shih et al.(49)	MV >48 hours, LCOS	12-hr postoperative BNP	Cut-point 540pg/ml predicted MV> 48hours (AUC 87.7%, 95%

			CI 76.8-96.8, sensitivity 88.9%, specificity 82.5%, p=0.0002). Cut-point 815 pg/ml predicted LCOS (AUC 91.4%, 95% CI 80-100, sensitivity 87.5%, specificity 90.2%, p=0.0001).
Amirnovin et al.(26)	Major poor outcome defined as death or need for unplanned surgical intervention.	Absolute peak postoperative BNP level and post- to preoperative ratios.	BNP levels were significantly higher in patients with vs without major poor outcome (1776+/-329pg/ml vs 1159+/-204pg/ml, p=0.04; 1215+/-375pg/ml vs 492+/-62pg/ml, p=0.04; 476+/-73pg/ml vs 368+/-40pg/ml, p=0.04 in patients with UH, LRS and ToF, respectively). In these three groups patients with worse outcome had significantly higher postoperative to preoperative BNP ratios.
Berry et al.(28)	Hospital LOS, inotropic requirement	6- to 12-hr postoperative BNP	BNP correlated with LOS in hospital (p=0.005) and inotropic requirement (p=0.01).
Hsu et al.(38)	Adverse outcome defined as death/ surgical intervention; LCOS; MV	12-hr postoperative BNP	BNP >500pg/ml predicted adverse outcome in the BCPA group (AUC 0.81,p=0.03). BNP was not predictive of outcome in the 11 TCPC patients.
Walsh et al.(17)	Inotropic use and dosage, MV,	Peak BNP (12 or 24 hrs	Levels correlated with inotropic use and dosage

	PICU LOS and hospital LOS	postoperatively)	(r=0.460,p=0.004), MV (r=0.454,p=0.004), PICU LOS (r=0.492,p=0.002) and hospital LOS (r=0.571,p=0.0002).
Cannesson et al.(53)	Complicated postoperative evolution defined as MV or LCOS for more than 72hours.	6-hr postoperative BNP	Cut-point of 160pg/ml predicted a complicated postoperative evolution (AUC: 0.82, sensitivity: 93%, specificity: 67%).

Table 4. Summary of studies showing positive association between postoperative NP levels and early postoperative outcome

Abbreviations used as in Table 3.

AUC: area under the curve; CI: confidence interval; ECLS: extracorporeal lifesupport; LRS: left-to-right shunt; UH: univentricular heart; ToF: Tetralogy of Fallot.

Author	Outcome measure	Findings
Lowenthal et al.(21)	Cardiac failure	AUC 83% (95% CI 71-95)[a] Screening cut-point: 6.75pg/ml[b] General optimal cut-point: 25.1pg/ml[c] Diagnostic cut-point: 86.8pg/ml[d]
Ohuchi et al.(45)	NYHA functional class	NYHA II 43+/-62pg/ml vs NYHA III-IV 127+/-148pg/ml, p<0.001.
Atz et al.(25)	Systemic ventricular EF	Age- and gender-adjusted logBNPs higher in patients with poorer ventricular performance (EF<53%), p=0.02.
Man et al.(44)	Diastolic dysfunction	BNP levels correlated significantly with severity of diastolic dysfunction.
Koch et al.(42)	AV regurgitation and other *specific sequelae*	BNP levels in patients with vs without *specific sequelae*: 18pg/ml,IQR 12-69 vs 12pg/ml,IQR 6-21, p=0.003. Positive correlation with AV regurgitation (r=0.38,p=0.002).
Hager et al.(35)	Maximal exercise capacity	NT-proBNPs significantly higher in patients with VO_2max <14ml/kg/min vs those with VO_2max >14ml/kg/min: median 213pg/ml, IQR 99–459 vs median 79pg/ml, IQR 45-167, p=0.013.

Table 5. Summary of findings from studies reporting on the long-term outcome of patients with palliated UHs

a. ROC curve analysis was performed based on the individual patient data supplied by the authors, b. The screening cut-point was chosen with a sensitivity of 94% while optimising

specificity, c. The general optimal cut-point was chosen using the method that minimizes the mathematical distance between the ROC curve and the ideal point (sensitivity = specificity =1). An alternative method uses the Youden index. Using this method we arrived at the same cut-point of 25.1pg/ml. This method is preferred particularly when appropriate classification (or sensitivity) is given a higher priority than minimizing misclassification (or specificity)(22), d. The diagnostic cut-point was chosen with a specificity of 94% while optimising sensitivity.

Abbreviations used as in Table 4.

AV: atrioventricular valve; EF: ejection fraction; IQR: interquartile range; VO_2max: peak oxygen uptake.

Author	Outcome measure	Findings
Çetin et al.(30)	PR severity RVEDV	BNP correlated with PR severity: moderate PR (n=14) mean 20.5pg/ml+/- 9.1 vs severe PR (n=11) mean 38.2pg/ml +/-33.1, (r=0.4,p=0.0001). BNP correlated with RVEDV (r=0.7,p=0.0001).
Koch et al.(54)	PR severity	BNP correlated with PR severity[a]: Grade I (38% of patients) median 17pg/ml (IQR 10-37), Grade II (34%) 23pg/ml (IQR 12-38), Grade III (23%) 25pg/ml (IQR 15-43) and Grade IV(5%) 39pg/ml (IQR 27-77), (r=0.20, p=0.029).
Ishii et al.(39)	PR severity Exercise capacity	BNP correlated with PR severity: mild PR (n=9) 24pg/ml+/-17, moderate PR (n=7) 35pg/ml+/-17, severe PR (n=10) 69pg/ml+/-41, p<0.05. *BNP rise with exercise significantly higher in ToF* patients than in controls: 15pg/ml+/-12 vs 2pg/ml+/-2, p<0.01.
Pietrzak et al.(47)	PR severity Exercise capacity	NT-proBNP correlated with PR severity: mild/moderate PR (n=11) 35.5pg/ml[b]+/-32.9 vs severe PR (n=9) 157.3pg/ml+/-126.8, p<0.05. This significant difference persisted after maximal exercise (p<0.005)
Khositseth et al.(40)	RV dilatation at rest	NT-proBNP significantly higher in patients with vs without RV dilatation[c] : 267 pg/ml+/-351 vs 48 pg/ml+/-28, p=0.004. Cut-point > 115pg/ml predictive of RV dilatation (AUC 0.87, sensitivity= 71%, specificity= 100%).

Luijenburg et al.(43)	RA emptying and RV filling	NT-proBNP significantly higher in patients with vs without abnormal RA emptying and restrictive RV filling: 135pg/ml+/-84 vs 59pg/ml+/-59,p=0.002 and 135pg/ml+/-84 vs 76pg/ml+/-76,p=0.015.
Wand et al.(55)	RVEF and RV size.	NT-proBNP had an inverse correlation with RVEF (r = -0.5, p=0.02) but no correlation with RV size.
Çetin et al.(31)	Exercise capacity	BNP rise with exercise significantly higher in ToF patients than in controls: 37.6pg/ml+/-27.5 vs 11.3pg/ml+/-4.5, p=0.0001.

Table 6. Summary of findings from studies reporting on the long-term outcome of repaired ToF patients

a. PR graded according to the colour-flow mapping of the regurgitant jet, b. converted from fmol/ml although reported by authors as fmol/L- it was not possible to verify from authors if this was an editing error, c. defined as RVEDV index > 108ml/m^2.

Abbreviations used as in Table 5.

PR: pulmonary regurgitation; RA: right atrial; RVEF: right ventricular ejection fraction; RVEDV: right ventricular end-diastolic volume.

Word count: (from introduction up to and including conclusion following examiner corrections)
3349

Part D: Appendices

1. This dissertation was submitted to Pediatric Anesthesia on the 27-09-2013

Appendix 1. Modified QUADAS checklist for the assessment of study quality

1. Was the spectrum of patients representative of the patients who will receive the test in practice? (i.e. the patients have structural congenital heart disease and are to have or have had surgical correction/palliation)
2. Is the reference standard likely to classify the target condition correctly? (i.e. clinical and echocardiography criteria used)
3. Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests? (i.e. NP level taken at time of preoperative and postoperative clinical/echocardiographic evaluation)
4. Did the whole sample or a random selection of the sample, receive verification using the intended reference standard? (all patients were evaluated clinically/ using echocardiography)
5. Did patients receive the same reference standard irrespective of the index test result? (differential verification avoided i.e. the pathology was present regardless of the NP result)
6. Was the reference standard independent of the index test (i.e. NP levels were not used in preoperative diagnosis)
7. Were the reference standard results interpreted without knowledge of the results of the index test? (NP results blinded to preoperative severity and postoperative outcome)
8. Were the index test results interpreted without knowledge of the results of the reference standard? (NP results interpreted blind of preoperative and postoperative findings)
9. Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (relevant clinical information including patient age)
10. Were withdrawals from the study explained? (e.g. follow-up loss)
11. Were cut-off values established before the study was started?

12. Is the technology of the index test unchanged since the study was carried out?
13. Did the study provide a clear definition of what was considered to be a 'positive' result?

Appendix 2 Study quality assessment scores*

Author	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total score (out of 13)
Amirnovin (2012)	1	1	1	1	1	1			1	1	1	1	1	11
Apitz (2009)	1	1	1	1	1	1			1	1		1	1	10
Atz (2011)	1	1			1	1			1		1	1	1	8
Berry (2008)	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Cannesson (2007)	1		1	1	1	1	1	1	1	1	1	1	1	12
Carmona (2008)	1	1	1	1	1	1			1	1	1		1	10
Cetin (2008)	1	1	1	1	1	1			1	1		1	1	10
Cetin (2009)	1	1	1	1	1	1			1	1		1	1	10
Chikovani (2007)	1	1	1	1	1	1	1	1	1		1	1	1	12
Chow (2006)	1	1		1	1	1			1	1	1	1	1	10
Eerola (2010)	1	1	1	1	1	1			1	1		1	1	10
Garg (2008)	1	1	1		1	1			1	1			1	8
Hager (2012)	1	1	1	1	1	1			1	1	1	1	1	11
Holmgren (2007)	1	1	1	1	1	1	1	1	1		1	1	1	12
Holmgren (2008)	1	1	1	1	1	1	1	1	1	1		1	1	12
Hsu (2007)	1	1	1	1	1	1	1	1	1	1	1	1	1	13
Ishii (2005)	1	1	1	1	1	1	1	1	1	1			1	11
Khositseth (2007)	1	1	1	1	1	1	1	1	1	1		1	1	12
Knirsch (2008)	1	1	1	1	1	1			1	1	1	1	1	11
Koch (2006)	1	1	1		1	1			1		1	1	1	9
Koch (2007)	1		1	1	1	1	1	1	1	1	1	1	1	12
Koch (2008)	1	1		1	1	1			1	1	1	1	1	10
Koch (2010)	1	1	1	1	1	1			1	1	1	1	1	11
Lowenthal (2012)	1	1	1	1	1	1	1	1	1	1		1	1	12
Luijnenburg (2012)	1	1	1	1	1	1			1	1	1	1	1	11
Man (2010)	1	1	1	1	1	1			1	1		1	1	10
Niedner (2010)	1	1	1	1	1		1	1	1	1	1	1	1	12
Ohuchi (2004)	1	1	1	1	1	1			1				1	8
Paul (2009)	1	1	1		1	1			1	1		1	1	9
Pérez-Piaya (2011)	1	1	1	1	1	1			1	1	1	1	1	11
Pietrzak (2009)	1	1	1	1	1	1			1	1			1	9
Robbers-Visser (2009)	1	1	1	1	1	1			1	1	1	1	1	11
Shih (2006)	1		1	1	1	1	1	1	1	1	1	1	1	12
Sleeper (2006)	1	1		1	1	1			1				1	7

Tavli (2010)	1	1		1	1	1			1	1	1	1	1	10
Van den Berg (2009)	1	1	1	1	1	1			1	1	1	1	1	11
Wåhlander (2012)	1	1		1	1	1	1	1	1	1	1	1	1	12
Walsh (2008)	1	1	1	1	1	1	1	1	1	1		1	1	12
Wand (2007)	1	1	1	1	1	1			1	1		1	1	10

*see Appendix 1 for study quality checklist

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10. A reference list in Vancouver style (*Ann. Intern. Med.* 1997; 126: 36-47), in the order made in the text. Example: confirmed by other studies.[23] / [23] Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; 339: b2535.

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